Atty Dkt 9000-0030
PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:
Jiang et al.

Serial No.: 08/658,277 Group Art Unit: 1817
Filing Date: 10/15/92 Examiner: K. Masood
Title: CAMP FACTOR OF *STREPTOCOCCUS UBERIS*

Declaration of Andrew A. Potter, Ph.D.

I, Andrew A. Potter, declare as follows:

1. I received a Ph.D. in Microbiology from the University of Otago, Dunedin, New Zealand in 1981 and a B.Sc. degree in 1977 in Biology from Carleton University, Ottawa, Ontario, Canada. I am currently the Associate Director [Science] and a Senior Research Scientist at the Veterinary Infectious Disease Organization ("VIDO") at the University of Saskatchewan in Saskatoon, Saskatchewan ("the University"). I am also an Adjunct Professor at the Western College of Veterinary Medicine at the University. During my 13 years at VIDO, I have studied the mechanisms of pathogenesis of a number of veterinary bacterial pathogens and developed subunit vaccines for these pathogens, including the *Streptococcus uberis* vaccines described in the above-referenced patent application. I am therefore extremely familiar with *S. uberis*, as well as the CAMP factor from the organism, and the general knowledge in the scientific community regarding CAMP factors and uses thereof. A copy of my *curriculum vitae* is attached hereto as Exhibit A.

17, 1997 ("the Action") and the articles cited therein.

understand that the claims have been rejected over Jurgens et al., *J. Exp. Med.* (1987) 165:720-732 ("Jurgens"); Skalka et al., *Zentralbl. Bakteriol. Ser. A* (1981) 249:190-194 ("Skalka") both taken alone; and the combination of Jurgens or Skalka, in view of Schneewind et al., *Infect. Immun.* (1988) 56:2174-2179 ("Schneewind").

3. I do not agree that Jurgens, Skalka or Schneewind, taken alone or in combination, describe the invention as now claimed or render the present claims obvious, i.e., that the differences between the invention as claimed and the subject matter of the cited art are such that they would be obvious to one skilled in the art, such as myself, as of the filing date of the patent application or earlier. My opinion is based on the facts set forth below, my familiarity with the subject matter, and particularly derives from the surprising and unexpected finding that *S. uberis* CAMP factor is useful for immunizing against mastitis.

4. In particular, I participated in isolating the *S. uberis* gene, purifying the protein encoded by this gene, and formulating the protein into vaccine compositions. As explained in Example 1 of the application, the *S. uberis* CAMP factor was isolated from host cells expressing the same as inclusion bodies, using the techniques described in Rossi-Campos et al. (1992) *Vaccine* 10:512-518. The method entailed harvesting cells by centrifugation, resuspending and freezing cells at -70°C. The frozen cells were thawed at room temperature and lysozyme was added. A detergent mix was then added. The viscosity was reduced by sonication and protein aggregates were harvested by centrifugation. The pellets were dissolved in a volume of 4 M guanidine

vaccine compositions and administered to animals as detailed in Example 6 of the application. No protein refolding step was done prior to use of the purified CAMP factors.

5. The purification method described above denatures any proteins present, rendering them substantially non-cytolytic. A residual amount of activity may remain but not enough to render the compositions toxic, even at high doses. The proteins, however, maintain immunogenicity. This is significant because the compositions described in Jurgens and Skalka both clearly include toxic proteins. Vaccines formulated using the proteins described in the present application have the distinct advantage of lacking such toxicity. In fact, it would not be appropriate to administer the toxic compositions described in Jurgens and Skalka to animal subjects for the treatment or prevention of mastitis.

6. Furthermore, as explained above, the fact that the compositions of the present invention were useful against mastitis was unexpected in view of the state of the art at the time of the invention. In this regard, it was generally believed that a vaccine against mastitis caused by a gram-positive bacterium such as *S. uberis*, was not feasible. Attached hereto as Exhibit B is Anderson, J.G., *Br. Vet. J.* (1978) 134:412-420 ("Anderson"), an article which pertains to staphylococcal mastitis, also caused by a gram-positive bacterium. The discussion in the article is equally relevant to streptococcal mastitis. As explained at page 416 of Anderson, top of page, as well as in the conclusion, invasion of the mammary gland by these bacteria results in an inflammatory response thereby increasing the somatic cell

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However, the inflammatory response is also the basic mechanism by which an organism protects itself against disease. Therefore, the very act of immunization would logically lead to enhanced somatic cell counts and, by definition, constitute mastitis. The authors, at page 417, last sentence of the first full paragraph, state: "It seems unlikely, therefore, that a protective mechanism can be developed which depended only on specific antibacterial antibody, even if that antibody could be transported across an intact secretory epithelium." In the last sentence of the paper the authors state: "Only when protection can be achieved by eliciting an inflammatory response which is insufficient to constitute subclinical mastitis, will immunization against bovine mastitis have succeeded."

7. We have been successful in developping such a vaccine. As is evident, this success was contrary to the general belief at the time that mastitis was not a disease that could be prevented using immunization.

8. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date Feb 10, 1998

Andrew A. Potter, Ph.D.